Review

Fetal origins of insulin resistance and the metabolic syndrome: A key role for adipose tissue?

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Abstract

For several years now, the epidemiological data have shown an inverse relationship between birth-weight and the development in later life of cardiovascular disease and metabolic disorders. The term “small for gestational age” (SGA) describes a neonate whose birth-weight is two standard deviations (SD) below the reference mean, corrected for gestational age and gender. SGA is associated with increased risks of developing hypertension, insulin resistance and type 2 diabetes. However, the association with an atherogenic lipid profile is less clear. Nevertheless, all of the components of the metabolic syndrome are present. Yet, in spite of the large body of data in the literature, the biological mechanisms underlying this association are still unclear. To explain the association, various hypotheses have been proposed, pointing to the role of a detrimental fetal environment or genetic susceptibility, or interaction between the two, and to the particular dynamic changes in adiposity that occur during catch-up growth. However, not only quantitative, but also qualitative, abnormalities of adipose tissue have been observed, suggesting a critical role of this organ in the development of metabolic complications.

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Keywords: SGA; Low-birth-weight; Catch-up growth; Metabolic syndrome; Adipose tissue; Review

Résumé

Contribution de l’environnement intra-utérin au développement de l’insulinorésistance et du syndrome métabolique à l’âge adulte : rôle clé du tissu adipeux ?.

Une corrélation négative entre le poids de naissance et la mortalité cardiovasculaire a été mise en évidence pour la première fois voici bientôt 20 ans. Depuis, de nombreuses études sont venues confirmer ce résultat. Le petit poids de naissance est défini comme un poids et/ou une taille de naissance inférieur(e) à deux écart-types, rapporté pour l’âge gestationnel et selon la distribution de référence. Le petit poids de naissance pour l’âge gestationnel est aussi lié au développement d’une HTA, d’une obésité, d’une insulinorésistance, voire d’un diabète de type 2. L’effet sur le profil lipidique semble plus modeste. Ainsi, les différents composants du syndrome métabolique sont liés à l’antécédent de petit poids de naissance. Plusieurs mécanismes physiopathologiques ont été proposés pour expliquer les liens entre le petit poids de naissance et le développement, à l’âge adulte, de pathologies cardiovasculaires et métaboliques. Le rôle de l’environnement délétère intra-utérin ou celui des gènes de susceptibilité, voire l’association des deux, ont été évoqués. Le rattrapage pondéral, qui survient dans les premières années de la vie, semble largement contribuer à ces observations. Le lien avec l’index de masse corporelle (IMC) au moment de l’observation a été souligné. Le rôle de la croissance du tissu adipeux à la fois durant la période fœtale et postnatale semble déterminant pour le développement ultérieur de troubles métaboliques chez les sujets qui ont présenté un petit poids de naissance. L’adaptation de certains organes durant la vie fœtale pourraient devenir inappropriée une fois la période de restriction passée. Cependant, ces mécanismes restent pour le moment hypothétiques.

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Mots clés : Petit poids de naissance pour l’âge gestationnel ; Syndrome métabolique ; Rattrapage pondéral ; Tissu adipeux et composition corporelle ; Revue générale

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1. Introduction

The idea that fetal and early life events result in permanent alterations or developmental “programming” was first proposed by Barker et al. and Barker [1,2], following a series of epidemiological observations. In humans, the link between fetal undernutrition per se and long-term abnormalities in glucose regulation has been clearly demonstrated in the follow-up of individuals born during the Dutch famine of World War II [3]. Young adults, exposed in utero to the famine, demonstrated higher 2-h plasma glucose values after oral glucose challenge than did controls born either before, or conceived after, the famine. Furthermore, exposure to famine during the late gestational period was associated with the highest 2-h plasma glucose levels. Barker et al. [1] found a relationship between the environmental influences that impair growth and development in early infancy, and the risk of ischaemic heart disease. To test this hypothesis, 5654 men born between 1911 and 1930 in six districts of Hertfordshire, England, were traced, and their weight during infancy recorded. Those with the lowest weights at birth and at age of 1 year had the highest death rates due to ischaemic heart disease. Similarly, Hales et al. [4] found a relationship between a reduction in birth-weight and either glucose intolerance or type 2 diabetes. Using a definition of the metabolic syndrome based on the occurrence of glucose intolerance, hypertension and hypertriglyceridaemia, the prevalence of the syndrome—also called “syndrome X”—was six times higher in men aged 65 years than those who weighed 2.5 kg or less at birth compared with those who weighed 4.5 kg or more [5]. For several years now, many studies in different populations have confirmed these initial findings. Moreover, these studies have confirmed a strong association between low-birth-weight, and insulin resistance and other metabolic disorders.

2. Definition of “small for gestational age” (SGA)

To study the relationship between birth-weight and the development of metabolic disorders later in life, published reports have either considered birth-weight as a continuum or defined SGA as the consequence of a restrictive fetal environment. Traditionally, the term has been used to describe a neonate whose weight and/or crown–heel length at birth is at least two standard deviations (SD) below the mean for gestational age, based on data derived from an appropriate reference population. Some authors also define SGA as a birth-weight or length below the third or the 10th percentiles for gestational age. The term “intrauterine growth retardation” (IUGR) is often used interchangeably with SGA. However, as IUGR implies an underlying pathological process that prevents the fetus from achieving its usual growth potential, the term should be restricted to describing infants whose small size can be attributed to a specific (pathological) cause and whose prenatal growth has been confirmed by intrauterine growth assessments. As the factors influencing intrauterine growth are numerous, only the main causes are presented in Table 1.

3. Birth-weight and cardiovascular mortality

The suggestion that coronary heart disease might have its origins during fetal development arose from the similarity of the geographical pattern of death rates among babies in Britain during the early 1900s [6] and the pattern of today’s death rates from coronary heart disease. The usual certified cause of death in newborn babies at that time was low-birth-weight. Early epidemiological studies pointed to the possible importance of “programming” for coronary heart disease based on the examination of men and women in middle and later life whose body measurements had been recorded at birth. Altogether, 16,000 men and women born in Hertfordshire between 1911 and 1930 were traced from birth to the present day. Death rates from coronary heart disease were threefold higher in those at the lower end of both the weight range at 1 year of age and the birth-weight distribution (<8.1 kg) compared with those at the upper end of the weight range at age 1 year (>12.7 kg) [1].

The association between low-birth-weight and coronary heart disease has also been confirmed by studies carried out in Wales [7] and among women in the United States. Of 80,000 women followed in the US Nurses’ Health Study, there was a fall in the relative risk of non-fatal coronary heart disease across the range of birth-weights [8]. An association between low-birth-weight and the prevalence of coronary heart disease was also found in a study carried out in South India [9]. Among Indian men and women aged 45 years or older, the prevalence of heart disease fell from 18% in those who weighed 2.5 kg at birth to 4% in those

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**Table 1**

Factors associated with small for gestational age (SGA) births.

<table>
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<tr>
<th>Medical complications</th>
<th>Antiphospholipid syndrome</th>
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<td>Preeclampsia</td>
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<td>Acute or chronic hypertension</td>
<td>Malignancy</td>
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<td>Antepartum haemorrhage</td>
<td>Uterine abnormalities</td>
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<td>Severe chronic disease</td>
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<td>Maternal social conditions</td>
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<td>Malnutrition</td>
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<td>Low pregnancy body mass index</td>
<td>Alcohol abuse</td>
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<td>Low maternal weight gain</td>
<td>Illicit drug use</td>
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<td>Low socioeconomic status</td>
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<td>Fetal conditions</td>
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<td>Inborn errors of metabolism</td>
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<td>Intrauterine infection</td>
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<td>Environmental factors</td>
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<td>Toxic substance use (such as tobacco)</td>
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<td>Placental abnormalities</td>
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<td>Reduced blood flow</td>
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<td>Reduced area of exchange</td>
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<tr>
<td>Infarction</td>
<td>Partial abruption</td>
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who weighed 3.2 kg or more. In addition, thinness at birth, as determined by a low ponderal index (birth-weight/length³), was also associated with coronary heart disease. Similarly, among men born in Helsinki, Finland, low-birth-weight was associated with higher death rates due to coronary heart disease, with a strong association with thinness at birth, especially in men who had been carried to term [10].

In three of the studies that have replicated the association between birth-weight and coronary heart disease, data on lifestyle factors—including smoking, employment, alcohol consumption and exercise—were also collected [7]. These findings suggest that factors influencing early fetal growth have an important effect on the risk of later coronary heart disease and stroke. In studies exploring the mechanisms underlying these associations, the trends linking coronary heart disease with birth-weight were found to parallel similar trends in two of its major risk factors: hypertension and type 2 diabetes [4].

4. Birth-weight and impaired glucose tolerance or type 2 diabetes

The association between birth-weight, impaired glucose tolerance and type 2 diabetes was first reported in Hertfordshire [4,11]. The prevalence of type 2 diabetes and impaired glucose tolerance was increased sixfold in individuals with a birth-weight less than 2.5 kg at birth compared with those whose birth-weight was greater than 4.5 kg [4]. Again, these associations with small size at birth were independent of social class, cigarette-smoking and alcohol consumption.

As insulin plays a central role in fetal growth, it is likely that disorders of glucose and insulin metabolism represent a possible link between early growth and cardiovascular disease. Although obesity and sedentary lifestyle are important in the development of type 2 diabetes, they appear to lead to the disease only in predisposed individuals. In the US Health Professionals Follow-up Study, the odds ratio (OR) for diabetes, adjusted for current body mass index (BMI), insulin resistance was greater in those whose birth-weight was greater than 4.5 kg [4]. Again, these associations with small size at birth were independent of social class, cigarette-smoking and alcohol consumption.

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4.1. Insulin secretion

Initially, it was proposed that impaired β-cell function might be involved in type 2 diabetes associated with low-birth-weight. However, clinical studies revealed no obvious primary deficit in insulin secretion in individuals born SGA. In a sample of 103 men and women who participated in a Preston, UK, study, Phillips et al. [11] measured insulin secretion following intravenous infusion of glucose. Insulin response was not related to birth-weight or any other measurements at birth. This argued against a link between reduced fetal growth and insulin deficiency in adult life. Similarly, a study of men in Stockholm found no association between birth-weight and insulin responses to infused glucose [15]. Likewise, Jaquet et al. [16] carried out a prospective follow-up study of young adults born in the city of Haguenau, France, which included 1600 individuals who were assessed at 22 and 29 years of age. These participants were selected according to their birth data in the maternity registry at Haguenau. The SGA group included all singletons born between 32 and 42 weeks of gestation with a birth-weight below the 10th percentile for gender and gestational age, according to the local standard growth curves. Those born “appropriate for gestational age” (AGA group) comprised singletons born between 32 and 42 weeks of gestation, with a birth-weight between the 25th and 75th percentiles, who were the first babies in the registry born immediately after an infant who was SGA. In this cohort at 22 years of age, on the basis of the acute insulin response to an intravenous glucose tolerance test, there was no evidence of any defect in insulin secretion in the SGA infants.

Recently, Freathy et al. [17] discovered that two alleles (CDKAL1 and HHEX-IDE) related to type 2 diabetes risk were also associated with reduced birth-weight. These loci have been shown to predispose to diabetes by reducing insulin secretion. This was the first evidence of a common genetic association between low-birth-weight and type 2 diabetes. However, the effect was weak, with a mean birth-weight difference of 80 g between carriers of the risk alleles compared with those who were not.

However, there are conflicting reports as to whether or not the β-cell mass is reduced in human fetuses born SGA [18]. In contrast, in animal models of IUGR or low-birth-weight, a primary defect in pancreatic development has been clearly demonstrated [19]. In rodents, experimental models of adverse fetal environment—induced by either caloric or protein restriction, restricted placental blood supply or exposure to high glucocorticoids—have all shown the same decreased β-cell mass and lower pancreatic insulin content.

4.2. Insulin resistance

Deficiencies in both insulin production and insulin resistance are thought to be important in the pathogenesis of type 2 diabetes [20]. Phillips et al. [11] carried out insulin tolerance tests in 103 men and women born in Preston. At any value of adult body mass index (BMI), insulin resistance was greater in those who had a low ponderal index at birth. In addition, at each ponderal index point, resistance was greater in those with a high
BMI. This suggests that the highest insulin resistance was in those of low ponderal index at birth, but high BMI as adults. A study carried out in San Antonio, Texas, [21] confirmed the association between low-birth-weight and insulin resistance in a different ethnic group. In 30-year-old Mexican-Americans and non-Hispanic Whites, those with lower birth-weights had a higher prevalence of the insulin resistance syndrome. Among men and women in the lowest third of the birth-weight distribution and highest third of the current BMI, 25% had the syndrome. In contrast, none of those in the highest tertile of birth-weight and lowest tertile of current BMI showed insulin resistance. In the Haguenua cohort at age 22, those born SGA showed increased plasma insulin concentrations both during fasting and after a standard glucose challenge [22]. Moreover, the rate of impaired glucose intolerance was three times higher in the SGA group. When measured by hyperinsulinaemic–euglycaemic clamp in a subset of individuals, insulin sensitivity was decreased by about 20% in those born SGA. Their insulin resistance was moderate, and independent of the usual factors associated with insulin resistance such as BMI, age, smoking, oral contraception, and family history of diabetes and dyslipidaemia. Interestingly, insulin resistance affected approximately one-third of the cohort born SGA [16].

In fact, men and women exposed in utero to the Dutch famine provide direct evidence that fetal undernutrition can “programme” later insulin resistance and type 2 diabetes [3,23]. Individuals exposed to famine in utero had higher 2-h plasma glucose concentrations than those either born before or conceived after the famine. They also had higher fasting proinsulin and 2-h plasma insulin concentrations, suggesting insulin resistance.

Twin studies have provided yet another opportunity to study the impact of birth-weight on glucose metabolism or other components of the metabolic syndrome. Fetal growth restriction is more likely to occur in twins compared with singletons. In addition, two-thirds of monozygotic twins are monochorionic—sharing the same placenta and nutritive source—and, consequently, have a more adverse intrauterine environment compared with dizygotic twins (who have separate sacs). According to the fetal origins hypothesis, monozygotic twins may be more prone to develop metabolic abnormalities. Poulsen et al. [24] demonstrated an increase in area under the curve (AUC) for both plasma glucose and insulin concentrations in monozygotic twins during an oral glucose tolerance test (OGTT). Poulsen and Vaag [25] also found an impact of birth-weight, twin and zygotic status (each representing independent markers of an adverse intrauterine environment) on peripheral and hepatic insulin action.

During childhood, other researchers have reported an association between low-birth-weight and insulin resistance. Law et al. [26] reported an increase in 30-min plasma glucose concentrations in 7-year-old children born in Salisbury, UK, while Whincup et al. [27], studying British children aged 10–11 years, found that those who had lower birth-weights presented with increased plasma insulin concentrations, both fasting and after OGTT. Yajnik et al. [28] found that Indian children, aged 4 years and with low-birth-weights, had raised plasma glucose and insulin concentrations.

### 4.3. Mechanisms

The processes that link thinness at birth with insulin resistance in adult life are, as yet, not known. Babies born at term with a low ponderal index have reduced mid-arm circumferences, suggestive of less muscle bulk as well as less subcutaneous fat [29]. It is therefore possible that thinness at birth is associated with abnormalities in the structure and function of muscle sufficient to interfere with insulin promotion of glucose uptake. Hermann et al. [30] showed that low-birth-weight is associated with impaired insulin-stimulated glucose uptake in forearm tissue and decreased whole-body insulin-stimulated glycolytic flux, even before the development of whole-body peripheral insulin resistance [31], in 19-year-old healthy men. Moreover, they also found that low-birth-weight is associated with altered muscle-fibre distribution [32], and reduced basal expression, in muscle and adipose tissue, of glucose transporter 4 (GLUT4) as well as several key insulin-signalling proteins [33]. Indeed, these findings suggest the presence of multiple abnormalities in insulin-sensitive tissue before the onset of whole-body insulin resistance.

### 5. Association between birth-weight and hypertension

Associations between low-birth-weight and raised blood pressure in childhood and adult life have been demonstrated in studies carried out around the world. Law and Shiell published a systematic review of studies [34] describing the association between birth-weight and blood pressure, based on 28 studies that included more than 15,000 people of all ages and from many countries. In almost all the studies, an increase in birth-weight was associated with a decrease in blood pressure. Differences in systolic pressure for every 1-kg difference in birth-weight were estimated to be 2–4 mmHg. Huxley et al. [35], who updated these data with an additional 27 studies, found the inverse association unchanged at −2 mmHg/1 kg of birth-weight. Twin studies have further confirmed these data [36]. More recently, Huxley et al. [37] pointed out the role of adjusting for potential confounding factors. BMI remains an important influence on blood pressure, with the highest blood pressures found in those who were small at birth, but who become overweight as adults.

#### 5.1. Mechanisms

The mechanisms involved in fetal programming of hypertension may be divided into renal and extrarenal processes [38]. A reduction in nephron numbers has been observed in animal models and on human autopsies [39]. Another important candidate is the renin–angiotensin–aldosterone system (RAAS). Animal experiments have revealed increased renal renin expression [40].

Increased mineralocorticoid activity of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) has also been implicated. This enzyme, located in the renal distal tubular cells, converts active cortisol into inactive cortisone. Under physiological circumstances, this protects the mineralocorticoid receptor from stimulation by cortisol. Indeed, in the IUGR rat model, renal...
11β-HSD2 expression is reduced, allowing for more mineralocorticoid activity of the enzyme. Interestingly, there is a reduction of 11β-HSD2 in the human placenta in pregnancies complicated by IUGR. This suggests that maternal cortisol, which is usually inactivated by placental 11β-HSD2, can be passed on to the fetus. As a consequence, cortisol may lead to growth restriction and possibly to programming of the renal 11β-HSD2 in the unborn child [41,42].

In addition to renal mechanisms, extrarenal alterations have also been investigated. One interesting area in this respect is the endothelium, and its interaction with vascular smooth muscle. Some findings suggest a role for the nitric-oxide (NO) system [38].

An increased sympathetic neural activity has also been implicated, given the relationship between birth-weight and basal heart rate in adults [43]. This hypothesis is further supported by animal data showing that denervation of the renal sympathetic nerve supply leads to normalization of blood pressure in low-birth-weight rats [44]. Certainly, the mechanism is not exclusively extrarenal, as sympathetic nerve activity regulates renin synthesis and salt retention in the kidneys. Also, in animal models, there is evidence of an impaired vascular structure [45].

6. Association between birth-weight and dyslipidaemia

Data from the literature are conflicting, and fail to demonstrate a robust association between birth-weight and serum lipid profiles. However, the information available is sparse and difficult to compare because of the wide differences in study populations in terms of age, gender and ethnic or genetic background. A meta-analysis by Lauren et al. [46] failed to strongly support a link between small size at birth and blood lipid levels in later life. In their review, the authors included 39 published studies involving both children and adults, but could find no consistent relationship between birth-weight and blood lipid concentrations, with the possible exception of a negative association between birth-weight and triglycerides. Data from a Helsinki study [47] showed a weak association between birthweight and dyslipidaemia. A 1-kg/m² lower BMI at birth was associated with a 0.051-mmol/L higher non-HDL-cholesterol level and a 0.018-g/L higher apolipoprotein-B concentration. Those exposed to Dutch famine during early gestation were twice as likely to consume a high-fat diet (defined as the highest quartile of fat percentage in the diet, with greater than 39% of energy derived from fat). This may, in part, explain their more atherogenic lipid profile, as found in the Dutch famine study [48].

7. Association between the metabolic syndrome and birth-weight

The metabolic syndrome refers to a constellation of hypertension, dyslipidaemia (high serum triglyceride and low HDL-cholesterol concentrations), elevated blood pressure and abdominal obesity. Since the first observations by Barker et al. [5], other investigators studying various different populations have similarly reported an association between low-birth-weight and increased risk of the metabolic syndrome as adults. In the Haguenau cohort, at 22 years of age, 2.3% of individuals born SGA were affected by the metabolic syndrome compared with 0.3% of the AGA group [22]. However, because of the lack of an accepted definition, most of the studies differed in their definition of the syndrome [5,49,50], making direct comparisons difficult. Valdez et al. [21] demonstrated that young, normotensive, non-diabetic adults with birth-weights in the lowest tertile had significantly higher fasting serum insulin concentrations, more truncal fat deposition and increased serum triglycerides. The metabolic syndrome prevalence was also 1.72 times greater for each tertile decrease in birth-weight. In this study too, those in the lowest tertile who were later in the highest tertile of BMI as adults had the highest prevalence of the metabolic syndrome. In postmenopausal women aged 54–84 years, those in the lowest tertile of birth-weight exhibited an increased prevalence (12% vs 4.3%, P<0.05) and twice the risk of developing the syndrome [51]. Indeed, women in the lowest birth-weight tertile who were in the highest tertile of BMI as adults had the highest prevalence of the metabolic syndrome. In that study, birth-weight—according to multivariate analyses adjusted for age and obesity—was significantly associated with lower HDL cholesterol and higher triglyceride concentrations, and an increased waist circumference. In the Atherosclerosis Risk in Young Adults (ARYA) study [52] involving 744 young adults, aged 26–31 years, the authors found that those in the lower tertile of birth-weight had a higher risk for the metabolic syndrome, even after adjustment for gender, cardiovascular disease, family history and current education level (OR: 1.4, P=0.064), while birth-weight was also inversely correlated with systolic blood pressure and triglycerides. In the Dutch famine study [49], prenatal exposures to famine or reduced birth-weight were not associated with a significantly greater prevalence of the metabolic syndrome. However, some elements of the syndrome were associated with lower birth-weights, including an increase in systolic blood pressure or triglyceride levels, and a decrease in HDL cholesterol. These results suggest an interaction between low-birth-weight and later BMI as adults in the development of components of the metabolic syndrome.

8. Association between birth-weight and body composition

8.1. Adipose tissue development and body composition in SGA individuals

It is well established that adipose tissue plays a key role in the development and worsening of insulin resistance and other metabolic disorders. Reduced fetal growth severely alters the perinatal development of adipose tissue (Fig. 1). SGA newborns show dramatically reduced body fat mass at birth, while the vast majority of low-birth-weight infants go on to show postnatal catch-up growth, mostly during the first 6–12 months of life. This particular growth pattern, rather than the previous antenatal restrictions on their own, might be an explanation of the metabolic and clinical consequences described above.
The Dutch famine studies have clearly illustrated the link between altered fetal growth induced by prenatal conditions of famine and increased risk of obesity [53]. In the Leger et al. cohort [54], catch-up in height was not significantly related to either insulin resistance or metabolic syndrome parameters. However, in contrast, catch-up in BMI was significantly associated with an increase in metabolic syndrome markers, and was also inversely related to BMI at birth. However, individuals who expressed greater catch-up were not obese as young adults [22].

Recently, in 252 children in the Generation R study, Ay et al. [55] showed that, at 6 months of age, fat mass accumulation was significantly associated with either a slowdown in weight during the third trimester of fetal life or postnatal catch-up within 6 weeks of birth. In addition, Beltrand et al. [56] demonstrated a greater change in BMI z-scores at 4 months of life in neonates with fetal growth restriction compared with those without restriction. Such a growth pattern results in the restoration of BMI and fat mass. Interestingly, these results were independent of calorie intake. Furthermore, the same team also pointed out the importance of fetal growth restriction in the development of adaptive changes in body composition and metabolism [57].

These results demonstrate the limits of birth-weight as reflections of fetal growth restriction and might indicate that excessive weight gain after a period of growth restriction is possibly damaging. To better understand this phenomenon, various experimental models have been proposed. In rodent models, Dulloo et al. [58] demonstrated that the process of catch-up growth is characterized by a disproportionately greater rate of fat deposition relative to lean tissue. This state of preferential fat catch-up is brought about, at least in part, by suppression of thermogenesis, as suggested in animal models [59], and is associated with skeletal muscle insulin resistance. Suppression of thermogenesis precedes the appearance of excess body fat, central fat distribution and increased intramyocellular triglycerides or circulating lipid concentrations. The redistribution of glucose from skeletal muscle to adipose tissue during fat catch-up may explain the later development of metabolic disorders [60].

In fact, most of the data on body composition in SGA subjects suggest that, despite a similar BMI, the SGA individuals had a greater percentage of body fat than those born AGA as either young adults (19 and 22 years of age) or in older age (64–72 years) [61,62]. The present study group also reported an increased percentage of body fat in SGA young adults (Fig. 2) [63,64]. However, those who experienced greater catch-up were not obese, suggesting that fat distribution is more crucial than weight per se. In addition, not only the percent body fat, but also the fat distribution appears to be influenced by the fetal environment, as some authors have reported that poor fetal growth is associated with increased abdominal fat later in life [65,66].

In a case-control study of 32, 64- to 72-year-old men with low and high birth-weights, the Hertfordshire study group—using dual-energy X-ray absorptiometry (DXA)—demonstrated that, after adjusting for weight and height, the low-birth-weight group had higher percentages of body fat and fat mass, less fat-free soft tissue and muscle mass, and a lower muscle-to-fat ratio. Such lifelong differences in body composition and fat distribution between the low- and high-birth-weight groups are consistent with programming in early life [62].

### 8.2. Respective roles of catch-up growth and later weight gain

Epidemiological data collected over the past 15 years have shown that size at birth, as well as early postnatal catch-up growth and excess childhood weight gain, may be a sequence that leads to central adiposity and insulin resistance [67].

On following SGA and AGA infants up to 6 years of age, Ibanez et al. [68,69] demonstrated that, consequent to catch-up weight gain between birth and age 2 years, SGA children showed a transition towards central adiposity and insulin resistance between ages 2–4 years. Between ages 4–6 years, the relative adiposity of SGA children was further amplified. Leunissen et al. [70] also showed, in 217 young SGA adults, that rapid
weight gain in the first 3 months of life was associated with an unfavourable metabolic profile and a higher percentage of body fat. The same team had previously reported that young adults born SGA with catch-up growth between birth and adulthood had higher risk factors for metabolic disorders, whereas those without catch-up growth had no increased risk [71]. Meriç et al. [72] studied 55 SGA and 13 AGA children from birth to 3 years of age. At age 3, the SGA children had restored their BMI. In these cases, the weight gain between birth and age 3 was the most important predictor of the later development of insulin resistance, as confirmed by HOMA-IR.

These data suggest that excessive weight gain after a period of growth retardation in early life might explain the risk of metabolic disorders later in life. However, other data emphasize influences in adult life in addition to the effects of the intrauterine environment. The prevalence of impaired glucose tolerance, for example, is highest in those of low-birth-weight who became obese as adults [73,74]. Also, BMI remains an important determinant of blood pressure and, in both humans and animals, the highest blood pressures are found in individuals who were small at birth, but overweight as adults. This argues in favour of the fact that other factors, such as changes in body size beyond catch-up growth (during later childhood or the development of obesity as adults) may also play a key role.

Data from a Finnish cohort reveal that the highest rates of coronary heart disease were observed in those who were thin at birth, but whose weight was caught-up during childhood (at ages 2–7 years) [75]. Such an interaction between birth-weight and subsequent gain in BMI or fat mass, as well as current obesity, has also been described for insulin resistance, systolic blood pressure and serum cholesterol in 8-year-old Indian children [76,77] and a cohort of 20-year-old South Africans [78].

In the Dutch famine cohort [49,79], subjects were studied at age 50 and 57. The authors found that those of low-birth-weight had a greater age-related progression of glucose intolerance, and a large part of the decline was attributed to an increase in BMI.

Meas et al. [63] demonstrated that, during 8 years of follow-up, adults born SGA gained more in BMI than AGA, resulting in greater fat mass and more abdominal fat. These data suggest that the consequences of fetal growth restriction on body composition extend beyond the period of early postnatal catch-up.

8.3. Key role of adipose tissue?

In the Haguenau cohort, several findings point to the abnormal function of adipose tissue in SGA individuals. First, early insulin resistance of adipose tissue was observed, while normal glucose tolerance was preserved [16]. Also, there was decreased peripheral glucose uptake under hyperinsulinaemic–euglycaemic clamp that correlated closely with altered antilipolytic insulin activity, as assessed by reduced suppression of free fatty acid production during the clamp. Second, regulation of leptin production was altered in SGA subjects during both the catch-up growth period and adulthood [64]; similar results were observed for adiponectinaemia. In addition, adiponectin concentrations were reduced in the SGA compared with AGA children—to even lower than in obese children of the same age—and were inversely related to weight gain [80]. Third, abdominal subcutaneous tissue showed hyperresponsiveness to catecholamines [81] and, finally, insulin resistance as adults was modulated by genetic polymorphisms of key factors found in adipocytes, such as peroxisome proliferator-activated receptor γ and β3-adrenoreceptors [82].

Indeed, in animal models, alterations in adipose tissue have been described. Isgnaitis et al. [83] used a rat model of low-birth-weight induced by maternal calorie restriction, and found that the low-birth-weight pups with catch-up growth had greater adipose tissue mass than did the controls, similar to human catch-up fat phenotypes. In this animal model, however, preventing the pups’ catch-up growth also prevented their subsequent development of obesity and type 2 diabetes as adults [84]. Furthermore, it was also demonstrated that catch-up growth resulted in several dominant fat patterns such as increased adipocyte size, and up-regulation of the key genes controlling the flux of glucose towards lipogenesis, despite the unaltered expression of genes implicated in adipocyte differentiation/proliferation. Interestingly, there was no proinflammatory profile or alteration of insulin sensitivity. In this rat model, expression of both insulin receptors and GLUT4 was increased.

It is possible that whole-body and tissue-specific insulin sensitivity varies throughout life, with early increases during lipogenesis and adipose tissue accretion, and subsequent reductions with ageing and weight gain. Guan et al. [85] used a different rat model of low-birth-weight induced by maternal protein restriction, and studied the visceral adipose tissue pattern of gene expression at 130 days of life. They found long-term consequences of fetal calorie restriction in the rats’ transcriptional profile of visceral adipose tissue. Fetal restriction induced and enhanced the expression of genes involved in regulating lipogenesis and angiogenesis, as well as the down-regulation of genes involved in the inflammatory process.

The role of local corticoid production has also been suggested. Although circulating cortisol concentrations are invariably normal in patients with obesity and the metabolic syndrome, in vitro, in vivo and clinical studies carried out over the last decade have collectively shown the importance of local cortisol generation via 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in the liver and fat [86]. 11β-HSD1 is a bidirectional enzyme that interconverts hormonally inactive cortisone to cortisol. Unlike cortisol, cortisone is not synthesized within the adrenal gland; its circulating pool of about 80 nmol/L is largely dependent on dehydrogenase activity (cortisol to cortisone) from the related 11β-HSD2 isozyme, expressed in the kidneys and gut. Nevertheless, the reductase activity of 11β-HSD1 can regenerate cortisol in tissues with high enzyme expression and, especially, in the liver and fat [87].

The abnormal regulation seen in the local metabolism of glucocorticoids appears to be an acquired phenomenon. Kannisto et al. [88] studied the effects of acquired obesity on the 11β-HSD1 gene (using real-time PCR) and protein (Western blot test) expression in subcutaneous adipose tissue in 17 monozygotic twin pairs, aged 24–27 years, who had a mean 3.8 kg/m² intra-pair difference in BMI (range: 0.4–10.1 kg/m²). They discovered that expression of 11β-HSD1 in subcutaneous adipose tissue is
increased in human acquired obesity, and is closely related to accumulation of subcutaneous and intra-abdominal fat, and features of insulin resistance. Furthermore, molecular screening of the 11β-HSD1 gene revealed no sequence variations that could have significantly contributed to the aetiology of the metabolic syndrome among French-Canadians or Pima Indians [89,90]. Nair et al. [90] studied two representative single-nucleotide polymorphisms of 11β-HSD1 and found an association with type 2 diabetes, although adipocyte 11β-HSD1 expression did not correlate with the genotypes of the donors. Indeed, muscle 11β-HSD1 messenger RNA (mRNA) concentrations did not correlate with any clinical or metabolic variables. This suggests that it is possible that the 11β-HSD1 gene is under tissue-specific regulation and has tissue-specific consequences.

Experimental evidence shows that changes in the environment during the perinatal period can affect the regulation of both metabolic and hormonal processes in adulthood, leading to programming of metabolic and cardiovascular diseases. Programming of corticotropic function—and, notably, the local metabolism of glucocorticoids—is possible through the use of nutritional and pharmacological perinatal interventions. In animals, it is possible to programme an enhanced response to stress and, in adipose tissue at the peripheral level, to induce increased local glucocorticoid exposure and sensitivity [91].

In sheep, maternal nutrient restriction is followed by IUGR in the ewes and modification of the local metabolism of glucocorticoids in adipose tissue. Tomlinson et al. [87] investigated the effects of such maternal nutrient restriction during the period of rapid placental growth on fetoplacental growth, and on the expression of glucocorticoid receptor (GR) types 1 and 2, 11β-HSD1 and 11β-HSD2, in the fetal and neonatal offspring. GR mRNA expression in the neonatal offspring of nutrient-restricted ewes was increased in the adrenals, kidneys, liver, lungs and perirenal adipose tissue. In contrast, 11β-HSD1 mRNA expression was unaffected except in perirenal adipose tissue, where it was higher in lambs born of nutrient-restricted ewes. Persistence of tissue-specific increases in the expression of GR, 11β-HSD1 and angiotensin II type 1 (AT1), and decreases in the expression of 11β-HSD2 in the adrenals and kidneys of newborn offspring in response to a defined period of maternal nutrient restriction during early to middle gestation, suggest that gene expression has been programmed by nutrient availability to the fetus prior to birth. Indeed, these results have also been confirmed by another group [92].

These observations suggest that adipose tissue is altered during fetal growth restriction and that the alteration extends into the postnatal developmental period. The resulting changes in adipose tissue have long-term functional consequences in adults. Adipose tissue is known to regulate several key systems, including energy and metabolism regulation, and insulin sensitivity. Thus, it is conceivable that early modifications in adipose tissue may induce insulin resistance and metabolic complications.

9. Conclusion

Many studies worldwide have shown that low-birth-weight confers an increased risk for metabolic or cardiovascular disorders later in life. However, it appears that not all individuals with a low-birth-weight are at the same risk of developing such complications. It may be that those at particular risk had fetal growth restriction followed by postnatal catch-up growth. However, other data suggest that influences in adult life, in addition to the effects of the intrauterine environment, are also involved. This points to other factors, such as changes in body size beyond the catch-up growth period (during later childhood or with the development of obesity as adults), as possibly also playing key roles. Moreover, not only quantitative, but also qualitative, abnormalities of adipose tissue have been demonstrated, suggesting a critical role for this organ in the development of metabolic complications. These epidemiological data should lead to particular attention being paid to patients born SGA in clinical practice. As for the classical cardiovascular risk factors, birth-weight should now also be included and recorded. In addition, the prevention of obesity or central fat accumulation through physical activity and appropriate diet needs to be considered in the management of such patients.

10. Conflict of interest

The author declares no conflict of interest in connection with this report.

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